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Thermodynamic and kinetic study of the interaction between the Pt(II) centres in [Pt_2(*N*,*N*,*N*′,*N*′-tetrakis(2-pyridylmethyl)diamine)-$(H_2O)_2$]$^{4+}$. Influence of the bridging ligand

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A series of binuclear Pt(II) complexes were synthesized to investigate the influence of four different bridging diamines, *viz.* benzene-1,3-diamine, benzene-1,4-diamine, 1,3-propanediamine and 1,4-butanediamine, on the reactivity of the platinum centres in complexes of the type [Pt_2(*N*,*N*,*N*′,*N*′-tetrakis(2-pyridylmethyl)diamine)-$(H_2O)_2$]$^{4+}$ in comparison to the corresponding mononuclear complex, [Pt(bis(2-pyridylmethyl)amine)(H_2O)]$^{2+}$. The pK_a values for both deprotonation steps were determined, and the kinetics of the reaction with chloride was studied under pseudo-first order conditions as a function of chloride concentration and temperature. The results indicate that the electrophilicity of the binuclear complexes is higher than that of the mononuclear complex, which results in lower pK_a values, higher reaction rates and a decrease in $\Delta H^{\ddagger}$. In addition, the reactivity of one Pt(II) centre shows a clear dependence on the nature of the other Pt(II) centre, leading to different thermodynamic and kinetic properties for the first and second reaction steps. The interaction between the two Pt(II) centres mainly depends on the Pt–Pt distance and not on the aromatic or aliphatic nature of the bridging diamine group. Temperature dependent ^{1}H NMR-studies were performed on the [Pt_2(*N*,*N*,*N*′,*N*′-tetrakis(2-pyridylmethyl)-1,3-propanediamine)Cl_2]$^{2+}$ complex, and the results indicate that a non-symmetric, folded species of this complex dominates at low temperatures. This behaviour may account for the unusual behaviour of the corresponding diaqua complex.

Introduction

Following Rosenberg's discovery of the anti-tumour properties of Cisplatin (*cis*-[$PtCl_2(NH_3)_2$], *cis*-DDP) in 1969,[1] thousands of Pt compounds have been synthesized and evaluated as potential anti-tumour drugs. Initially, the design of new drugs concentrated mainly on direct *cis*-DDP analogues according to the set of structure–activity relationships summarized by Cleare and Hoeschele in 1973.[2–4] The requirements for a Pt(II) complex to show anti-tumour activity are accordingly: (a) *cis* geometry with the general formula *cis*-[$PtX_2(Am)_2$]; (b) Am = inert amine with at least one N–H function; (c) X = leaving group, anion with an intermediate binding strength to platinum and a weak *trans* effect to avoid labilization of Am. It has, however, become quite evident that mere analogues of Cisplatin will probably not offer any substantial clinical advantages over the existing drugs. To reduce the Cisplatin resistance and widen the overall spectrum of activity, non-classical Pt(II) anti-tumour complexes that do not adhere to the Cleare and Hoeschele parameters, have been developed.[4] Promising candidates among these complexes are bridged dinuclear or trinuclear Pt(II) complexes which can form DNA adducts that are not accessible to mononuclear Pt(II) complexes, such as 1,3- and 1,4-GG interstrand cross-links.[5–7] The nature of the bridging ligand varies significantly. Whereas reactions of DNA or GMP with dinuclear Pt(II) complexes bridged by bifunctional thioureas,[8] spermine and spermidine,[9] pyrazine[10] or substituted aliphatic diamines[11] were investigated recently, simple aliphatic diamine bridges still dominate the scene.[5–7,11–14]

Although the role of the bridge on the DNA binding properties and product formation has been investigated intensively and the results have been interpreted in terms of charge, hydrogen bonding, length and flexibility of the bridging ligand,[15] there is less data available on the influence of the bridge on the reactivity and thermodynamic properties of the two platinum centres. Such data is available in the case of [{*trans*-$PtCl(NH_3)_2$}$_2${μ-*trans*-$Pt(NH_3)_2(NH_2(CH_2)_6NH_2)_2$}]$^{4+}$ (BBR3464) which is currently in phase II clinical trials and its corresponding dinuclear complex [{*trans*-$PtCl(NH_3)_2$}$_2$(μ-$NH_2(CH_2)_6NH_2$)]$^{2+}$. It suggests that the reactivity and properties of the first platinum centre is independent of the state of the second and *vice versa*.[13,16] However, in other cases such an interaction of the two bridged Pt(II) centres has been observed.[11,17] There is not enough data in the literature on this topic to formulate a relationship between the reactivity of the two platinum centres and the nature of the bridging ligand.

In order to gain further insight into the role of the bridging ligand, the influence of four different bridges on the reactivity of each of the platinum centres of the binuclear complex, in comparison to the corresponding mononuclear complex, was investigated. The binuclear complexes [Pt_2(*N*,*N*,*N*′,*N*′-tetrakis(2-pyridylmethyl)benzene-1,3-diamine)$(H_2O)_2$]$^{4+}$ (**mPh**), [Pt_2(*N*,*N*,*N*′,*N*′-tetrakis(2-pyridylmethyl)benzene-1,4-diamine)-$(H_2O)_2$]$^{4+}$ (**pPh**), [Pt_2(*N*,*N*,*N*′,*N*′-tetrakis(2-pyridylmethyl)-1,3-propanediamine)$(H_2O)_2$]$^{4+}$ (**Pro**), [Pt_2(*N*,*N*,*N*′,*N*′-tetrakis(2-pyridylmethyl)-1,4-butanediamine)$(H_2O)_2$]$^{4+}$ (**But**) and the corresponding mononuclear complex, [Pt(bis(2-pyridylmethyl)-amine)(H_2O)]$^{2+}$, were synthesized. The variation of the bridging diamine spacer enabled a systematic study of the influence of chain length, flexibility and hybridization of the bridge (aliphatic or aromatic backbone) on the thermodynamic (pK_a value of coordinated water) and kinetic properties (substitution reaction with chloride) of the two platinum centres.

Experimental

Chemicals and ligands

The ligands *N*,*N*,*N*′,*N*′-tetrakis(2-pyridylmethyl)benzene-1,3-diamine[18] and *N*,*N*,*N*′,*N*′-tetrakis(2-pyridylmethyl)benzene-1,4-diamine[19] were synthesized according to published methods. All chemicals, including the ligand bis(2-pyridylmethyl)amine were obtained from Aldrich in the highest purity available and used without further purification. Ultra pure water was used for the kinetic as well as spectroscopic measurements.

***N*,*N*,*N*′,*N*′-Tetrakis(2-pyridylmethyl)-1,3-propanediamine·½H_2O (1) and *N*,*N*,*N*′,*N*′-tetrakis(2-pyridylmethyl)-1,4-butanediamine (2).** These ligands were synthesized following the general procedure described in the literature for *N*,*N*,*N*′,*N*′-

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tetrakis(2-pyridylmethyl)-1,2-ethanediamine.[20] To a solution of 1.97 g (12 mmol) 2-(chloromethyl)pyridinium chloride in H_2O (0.5 mL) 3 mL 20% NaOH were added with stirring under Ar. To the resulting red solution 3 mmol of the corresponding diamine, 3 mL 20% NaOH, and 0.08 mL of 25% hexadecyltrimethylammoniumchloride solution (commercially available) were added. The mixture was stirred vigorously for 24 h at room temperature. It was then extracted with CH_2Cl_2 (3 × 10 mL), the extract washed with 20 mL of H_2O and dried over Na_2SO_4. After evaporation of the solvent, **1** was obtained as a brown oil and **2** as a brown solid. Ligand **1** was purified by column chromatography (Al_2O_3, CH_2Cl_2:EtOAc = 1 : 1, first fraction) and ligand **2** was recrystallized from acetone, giving white solids in both cases.

1: Yield: 878 mg (2.0 mmol, 67%). Anal. Calc. for $C_{27}H_{30}N_6 0.5H_2O$: C, 72.45; H, 6.98; N, 18.78. Found: C, 72.62; H, 7.40; N, 18.26%. ^{1}H NMR (D_2O, 300.0 K): δ 8.48 (md, $^3J_{HH}$ = 4.9 Hz, 4H), 7.58 (dt, $^3J_{HH}$ = 7.9 Hz, 1.5 Hz, 4H), 7.41 (d, $^3J_{HH}$ = 7.9 Hz, 4H), 7.10 (mt, $^3J_{HH}$ = 6.4 Hz, 4H), 3.74 (s, 8H), 2.55 (t, $^3J_{HH}$ = 7.2 Hz, 4H), 1.80 (t, $^3J_{HH}$ = 7.2 Hz, 2H).

2: Yield: 509 mg (1.1 mmol, 38%). Anal. Calc. for $C_{28}H_{32}N_6$: C, 74.30; H, 7.13; N, 18.57. Found: C, 74.34; H, 8.20; N, 18.25%. ^{1}H NMR (D_2O, 300.0 K): δ 8.49 (d, $^3J_{HH}$ = 4.9 Hz, 4H), 7.62 (dt, $^3J_{HH}$ = 7.7 Hz, 1.65 Hz, 4H), 7.49 (d, $^3J_{HH}$ = 7.9 Hz, 4H), 7.12 (t, $^3J_{HH}$ = 6.0 Hz, 4H), 3.76 (s, 8H), 2.48 (s br, 4H), 1.51 (s br, 4H).

Synthesis of complexes

[Pt_2(*N*,*N*,*N*′,*N*′-tetrakis(2-pyridylmethyl)benzene-1,3-diamine)Cl_2]$(ClO_4)_2$ (**3**), [Pt_2(*N*,*N*,*N*′,*N*′-tetrakis(2-pyridylmethyl)-benzene-1,4-diamine)Cl_2]$(ClO_4)_2$ (**4**), [Pt_2(*N*,*N*,*N*′,*N*′-tetrakis-(2-pyridylmethyl)-1,3-propanediamine)Cl_2]$(ClO_4)_2$ (**5**), [Pt_2-(*N*,*N*,*N*′,*N*′-tetrakis(2-pyridylmethyl)-1,4-butanediamine)Cl_2]-$(ClO_4)_2$ (**6**) and the corresponding mononuclear complex [Pt(bis(2-pyridylmethyl)amine)Cl]ClO_4 (**7**) were all synthesized following the same procedure: To a solution of 200 mg (0.48 mmol) K_2PtCl_4 in 50 mL 0.01 M HCl, a solution of 0.24 mmol of the corresponding bridging ligand (*i.e.* 0.48 mmol of the bis(2-pyridylmethyl)amine) in 50 mL 0.01 M HCl was added. The mixture was refluxed for 24 h, filtered if necessary, and the product was precipitated by addition of 1 mL of saturated $NaClO_4$ solution. The resulting powder was filtered off, washed with H_2O, EtOH and Et_2O, and dried in vacuum. The resulting product was recrystallized from water if necessary.

3: Yield: 183 mg (0.162 mmol, 67%). Anal. Calc. for $C_{30}H_{28}Cl_4N_6O_8Pt_2$: C, 31.82; H, 2.49; N, 7.42. Found: C, 31.41; H, 2.37; N, 7.11%. ^{1}H NMR (D_2O, 300.0 K): δ 10.38 (s, 1H), 8.79 (d, $^3J_{HH}$ = 5.3 Hz, 4H), 8.01 (dt, $^3J_{HH}$ = 7.9 Hz, 1.5 Hz, 4H), 7.90 (dd, $^3J_{HH}$ = 8.2 Hz, 2.4 Hz, 2H), 7.64 (m, 5H), 7.32 (d, $^3J_{HH}$ = 7.9 Hz, 4H), 5.65 (d, $^3J_{HH}$ = 15.2 Hz, 4H), 5.19 (d, $^3J_{HH}$ = 15.2 Hz, 4H).

4: Yield: 114 mg (0.101 mmol, 42%). Anal. Calc. for $C_{30}H_{28}Cl_4N_6O_8Pt_2$: C, 31.82; H, 2.49; N, 7.42. Found: C, 31.53; H, 2.34; N, 7.26%. ^{1}H NMR (CD_3OD, 300.0 K): δ 8.89 (d, $^3J_{HH}$ = 4.8 Hz, 4 H, Pt satellites), 8.12 (t, $^3J_{HH}$ = 7.9 Hz, 4H), 8.04 (s, 4H), 7.56 (d, $^3J_{HH}$ = 7.5 Hz, 4H), 5.71 (d, $^3J_{HH}$ = 15.4 Hz, 4H), 5.33 (d, $^3J_{HH}$ = 15.7 Hz, 4H).

5: Yield: 109 mg (0.099 mmol, 42%). Anal. Calc. for $C_{27}H_{30}Cl_4N_6O_8Pt_2$: C, 29.52; H, 2.75; N, 7.65. Found: C, 28.83; H, 2.68; N, 7.33%. ^{1}H NMR (D_2O, 358.2 K), since there is a temperature dependent equilibrium between the symmetric and the non-symmetric species, only the main peaks and the expected integrals for the symmetric species (as it would exist at higher temperatures, but cannot be measured) are given: δ 8.59 (d, $^3J_{HH}$ = 4.9 Hz, 4H), 8.18 (q, $^3J_{HH}$ = 7.7 Hz, 4H), 7.60 (m, 8H), 8.12 (t, $^3J_{HH}$ = 7.9 Hz, 4H), 5.11 (m, 4H), 4.60 (m, 4H), 2.99 (m, 4H), 2.04 (s br, 2H).

6: Yield: 115 mg (0.105 mmol, 44%). Anal. Calc. for $C_{28}H_{32}Cl_4N_6O_8Pt_2$: C, 30.23; H, 2.90; N, 7.55. Found: C, 30.89; H, 2.87; N, 7.45%. ^{1}H NMR (D_2O, 300 K): δ 8.90 (d, $^3J_{HH}$ = 5.7 Hz, 4 H, Pt satellites), 8.10 (t, $^3J_{HH}$ = 7.9 Hz, 4H), 7.62 (m, 8H), 5.19 (d, $^3J_{HH}$ = 16.1 Hz, 4H), 4.60 (d, $^3J_{HH}$ = 15.8 Hz, 4H), 2.79 (s br, 4H), 1.81 (s br, 4H).

7: Yield: 195 mg (0.369 mmol, 77%). Anal. Calc. for $C_{12}H_{12}Cl_2N_3O_4Pt$: C, 27.29; H, 2.29; N, 7.95. Found: C, 26.88; H, 2.31; N, 7.68%. ^{1}H NMR (D_2O, 300 K): δ 8.80 (d, $^3J_{HH}$ = 5.9 Hz, 2 H, Pt satellites), 8.15 (t, $^3J_{HH}$ = 7.5 Hz, 2H), 7.63 (d, $^3J_{HH}$ = 8.2 Hz, 2H), 7.51 (t, $^3J_{HH}$ = 7.0 Hz, 2H), 4.88 (s, 4H).

Preparation of complex solutions

The desired solutions of the aqua complexes of **mPh**, **pPh**, **Pro** and **But** were prepared by dissolving a known amount of the chloro complex in 0.001 M trifluoromethanesulfonic (triflic) acid and adding a stoichiometric excess (with respect to chloride) of silver triflate (150–200%). The mixture was then stirred overnight at 40–50 °C. The precipitated silver chloride was filtered off, the pH of the remaining solution was adjusted to 10–11 by adding 0.1 M NaOH, which resulted in the precipitation of brown Ag_2O. The precipitate was then removed with a Millipore filter, and the remaining solution was acidified again to pH = 2.0 through the addition of triflic acid. The resulting solution was diluted with 0.01 M triflic acid to give the desired complex concentration of 0.1 mM. For the preparation of the solution of the mononuclear complex, the corresponding hydroxo complex was prepared as described elsewhere[21] and dissolved in 0.01 M triflic acid to give a final concentration of 0.2 mM. For all investigations, the (starting) pH of the solution was 2.0 and the ionic strength was adjusted to 0.01 M.

Instrumentation and measurements

NMR spectroscopy (Bruker Avance DPX 300) and a Carlo Erba Elemental Analyser 1106, were used for chemical analysis and characterization of the complexes. NMR measurements at elevated temperatures were performed on a Bruker Avance DRX 400 equipped with a Widebore magnet.

UV-Vis spectra for the determination of pK_a values were recorded on a Varian Cary 1G spectrophotometer equipped with a thermostated cell holder or on a Hewlett Packard 8452A Diode Array spectrophotometer with a thermo-electrical temperature controlled cell holder. The pH of the solutions was measured using a Mettler Delta 350 digital pH meter, equipped with a combined glass electrode. This electrode was calibrated using standard buffer solutions at pH 4, 7 and 9 obtained from Sigma. Spectrophotometric pH titrations of the complex solutions were performed with NaOH as the base at 25.0 °C. To avoid absorbance corrections due to dilution, a large volume (100 mL) of the complex solution was used in the titration. A change in pH from 2 to approximately 3 was achieved by addition of known amounts of crushed pellets of NaOH. The consecutive pH changes were obtained by dipping a needle first into a saturated solution of NaOH, 1 M or 0.1 M NaOH and afterwards in the complex solution. It was found that when the pH electrode (filled with NaCl instead of KCl to avoid precipitation of $KClO_4$) was dipped into the test solution for a longer time, it resulted in the formation of the chloro complex. It was therefore necessary to take 2 mL aliquots from the solution into narrow vials for the pH measurements, and was discarded after the measurement. Each pK_a titration was performed at least two times and an average of both values was taken.

Kinetic measurements on the mononuclear complex were performed on an Applied Photophysics SX 18MV stopped-flow instrument coupled to an online data acquisition system. The binuclear bridged complexes were studied on the same stopped flow instrument, but the data acquisition was performed with a J&M TIDAS 200–620 nm rapid scan detector combined with a J&M TIDAS V 3.0 lamp. At least 1000 spectra were recorded

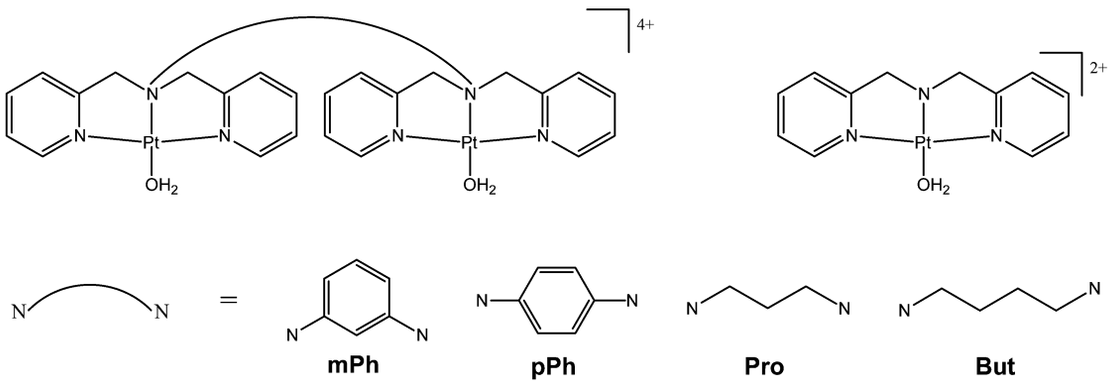

Fig. 1 Schematic structures and abbreviations used for the investigated complexes.

for each reaction, using two different time bases to have an equal amount of points for the fast and subsequent slow reaction steps. The ligand substitution reactions were studied under pseudo-first-order conditions. This was achieved by using at least a 20-fold excess of chloride compared to the concentration of the bridged complexes (*i.e.* a 10-fold excess compared to the concentration of the mononuclear complex). For the determination of the activation parameters, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, the rate constant for the reaction of each of the complexes with 3 mM chloride was measured as a function of temperature. All the reported rate constants represent an average value of at least six kinetic runs for each experimental condition.

Analysis of the time- and pH-dependent spectra was performed with Specfit [22] global analysis software. The temperature of the instruments was controlled within an accuracy of ±0.1 °C.

Results

In order to investigate the influence of chain length, flexibility and hybridization of the bridging ligand in the binuclear platinum complexes on the thermodynamic and kinetic properties of each of the two platinum centres, a total of four binuclear bridged complexes and their corresponding mononuclear complex were synthesized and characterized. Their schematic structures, together with the used abbreviations are summarized in Fig. 1. The similarities and differences between the aqua complexes of **mPh**, **pPh**, **Pro**, **But** and the mononuclear complex were first studied by determining the pK_a values of the coordinated water molecules, followed by a study of the ligand substitution reactions as a function of nucleophile (chloride) concentration and temperature. Both the kinetic as well as the thermodynamic data suggest that the properties of the two platinum centres are not independent of each other.

Acidity and formation of hydroxo complexes

A typical example of the spectral changes observed during the pH titrations is shown in Fig. 2. Eigen vector analysis with Specfit indicates that there are three coloured species in solution as a function of pH, proposing two distinguishable dissociation steps. The overall process can therefore be presented by reaction (1).

$$\begin{array}{c} H_2O\text{–Pt1–L–Pt1–}OH_2^{4+} + 2\ H_2O \\ \Updownarrow K_{a1} \\ HO\text{–Pt1–L–Pt2–}OH_2^{3+} + H_2O + H_3O^+ \\ \Updownarrow K_{a2} \\ HO\text{–Pt1–L–Pt2–}OH^{2+} + 2\ H_3O^+ \end{array} \qquad (1)$$

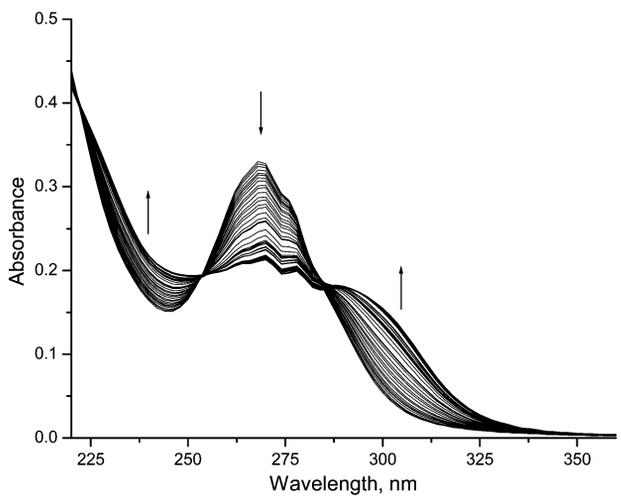

Fig. 2 UV-vis spectra for the **pPh** complex as a function of pH in the range 2–8; $I = 0.01$ M ($NaSO_3CF_3$), $T = 25.0$ °C.

According to this reaction scheme, the pH dependent spectra gave excellent fits to a model using two pH dependent steps with equilibrium constants K_{a1} and K_{a2}. The so obtained pK_a values for the coordinated water molecules on Pt1 and Pt2 are summarized in Table 1.

Kinetic measurements

The kinetic traces for the reaction between the mononuclear complex and chloride gave excellent fits to a single exponential, corresponding to reaction (2). In the case of the binuclear complexes **mPh**, **pPh**, **Pro** and **But**, a two exponential fit (A ⟶ B ⟶ C, reaction 3) had to be used to fit the observed time dependent spectra.

$$L\text{–Pt–}OH_2^{2+} + Cl^- \xrightarrow{k} L\text{–Pt–}Cl^+ + H_2O \qquad (2)$$

$$\begin{array}{c} H_2O\text{–Pt1–L–Pt2–}OH_2^{4+} + 2\ Cl^- \\ \downarrow k_1 \\ Cl\text{–Pt1–L–Pt2–}OH_2^{3+} + Cl^- \\ \downarrow k_2 \\ Cl\text{–Pt1–L–Pt2–}Cl^{2+} \end{array} \qquad (3)$$

The so obtained pseudo-first order rate constants, $k_{obs(1/2)}$, were plotted against the concentration of the entering chloride nucleophile. A linear dependence on the chloride concentration with no meaningful intercept was observed for all reactions. The corresponding plots for all bridged dinuclear complexes are shown in Figs. 3 and 4 for k_{obs1} and k_{obs2}, respectively. The results imply that $k_{obs(1/2)}$ can be expressed by eqn. (4).

$$k_{obs(1/2)} = k_{(1/2)}[Cl^-] \qquad (4)$$

Table 1 Summary of second-order rate constants and activation parameters for the displacement of coordinated water by chloride. The pK_a values for the first and second deprotonation steps of the aqua complexes are also included

	Mononuclear	**mPh**	**pPh**	**Pro**	**But**
pK_{a1}	5.5[a]	3.33	3.34	4.36	3.94
pK_{a2}	–	4.76	4.46	6.07	5.46
k_1/M^{-1} s^{-1}	19.1 ± 0.1	312 ± 6	265 ± 7	649 ± 38	249 ± 11
k_2/M^{-1} s^{-1}	–	24.4 ± 0.2	88 ± 1	132 ± 6	40 ± 1
$\Delta H^{\ddagger}_1$/kJ mol^{-1}	64.5 ± 0.1	55.1 ± 1.3	61.1 ± 1.8	63.8 ± 0.7	57.8 ± 0.8
$\Delta H^{\ddagger}_2$/kJ mol^{-1}	–	60.5 ± 0.9	60.5 ± 1.5	60.0 ± 0.8	57.7 ± 1.5
$\Delta S^{\ddagger}_1$/J K^{-1} mol^{-1}	−3.5 ± 1	−12 ± 4	5 ± 6	22 ± 2	−6 ± 3
$\Delta S^{\ddagger}_2$/J K^{-1} mol^{-1}	–	−15 ± 3	−6 ± 3	−4 ± 3	−21 ± 5

[a] Data taken from the literature.[21]

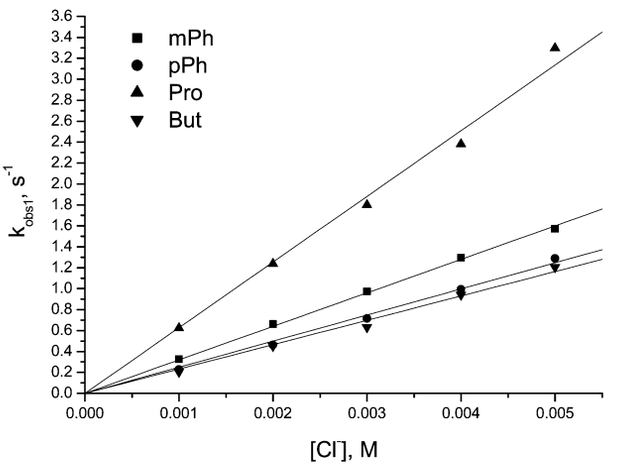

Fig. 3 Plots of k_{obs1} versus chloride concentration for the binuclear complexes: I = 0.01 M (HSO_3CF_3), T = 25.0 °C, pH = 2.0.

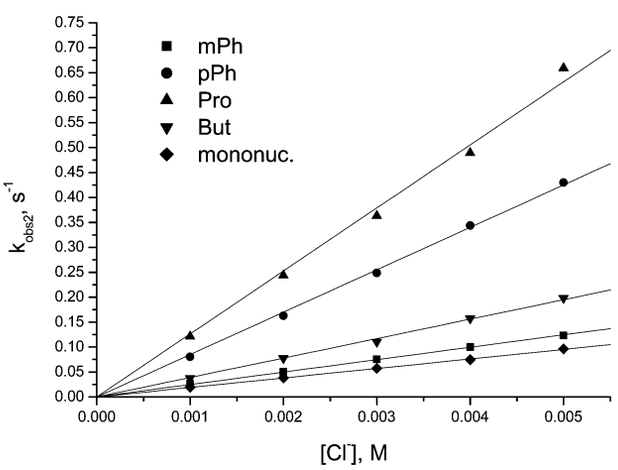

Fig. 4 Plots of k_{obs2} versus chloride concentration for the binuclear complexes and a plot of k_{obs} versus chloride concentration for the mononuclear complex: I = 0.01 M (HSO_3CF_3), T = 25.0 °C, pH = 2.0.

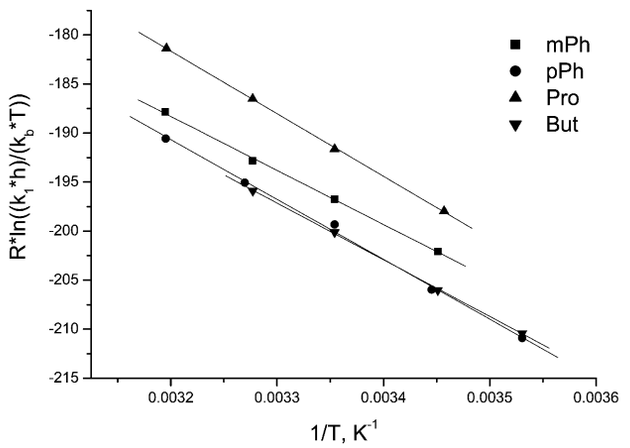

Fig. 5 Eyring plots for the determination of the activation parameters for the first substitution step of the binuclear complexes with chloride: I = 0.01 M (HSO_3CF_3), pH = 2.0.

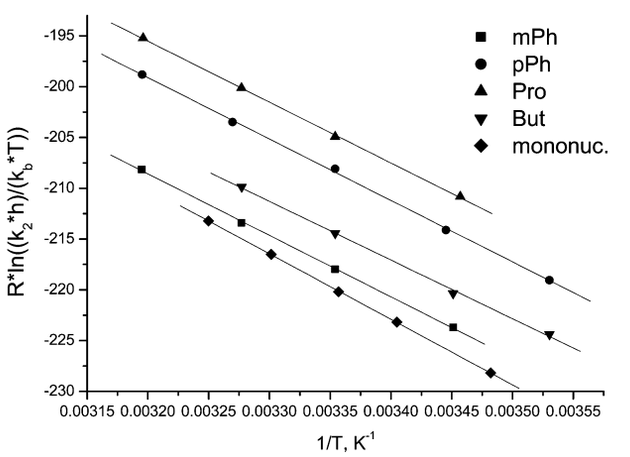

Fig. 6 Eyring plots for the determination of the activation parameters for the second substitution step of the binuclear complexes and for the reaction of the mononuclear complex with chloride: I = 0.01 M (HSO_3CF_3), pH = 2.0.

Since no meaningful intercept was observed, it must be concluded that the reverse reaction with water is too slow to contribute significantly to the values of $k_{obs(1/2)}$. The corresponding values of $k_{(1/2)}$ are summarized in Table 1. The thermal activation parameters, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, were calculated using the Eyring equation, for which the data are summarized in Table 1. The corresponding Eyring plots for the binuclear complexes are shown in Figs. 5 and 6 for k_1 and k_2, respectively.

Discussion

Comparison of pK_a values

We recently demonstrated that the pK_a value of a water molecule coordinated to Pt(II) can be used as a measure of the electrophilicity of the metal centre. Electron withdrawing π-acceptor effects stabilize the electron rich hydroxo species in comparison to the aqua complex and therefore lead to lower pK_a values.[21,23] On the other hand, the pK_a value increases if the σ-donor capacity of the *trans* ligand is enhanced.[24] Since it is known that the pK_a value of anilines is much lower than those of tertiary amines,[25] the higher basicity suggests that amines are better σ-donors than anilines. This apparently accounts for the fact that the pK_a values of the aniline bridged complexes **mPh** and **pPh** are lower (3.33/4.76 and 3.34/4.46, respectively) than those of the stronger σ-donating aliphatic diamine bridged complexes **Pro** and **But** (4.36/6.07 and 3.94/5.46, respectively).

The pK_a value for the first deprotonation step of all the binuclear complexes is at least 1.1 units lower than for the

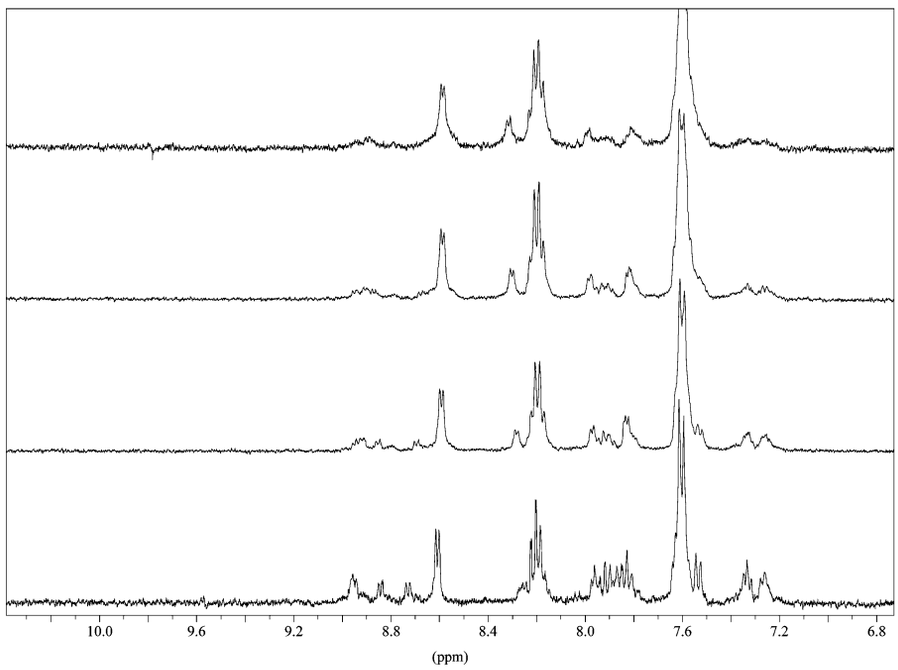

Fig. 7 Temperature dependent ^{1}H NMR spectra in D_2O of the aromatic region of the complex $[Pt_2(N,N,N',N'$-tetrakis(2-pyridylmethyl)-1,3-propanediamine)$Cl_2]^{2+}$. Measurements were taken at 25, 50, 70 and 85 °C (upwards). A decrease in the number of peaks is seen with increasing temperature, indicating that the equilibrium is shifted to a single symmetric species.

mononuclear complex (pK_a = 5.5). Similar effects have been observed for the pK_a values of the bridged complexes [{*trans*-$Pt(OH_2)(NH_3)_2\}_2$\{μ-*trans*-$Pt(NH_3)_2(NH_2(CH_2)_6NH_2)_2\}]^{6+}$ (**1,0,1/t,t,t**) and [{*trans*-$Pt(OH_2)(NH_3)_2\}_2$(μ-$NH_2(CH_2)_6NH_2)]^{4+}$ (**1,1/t,t**), where the values are about 0.4 units lower than for the corresponding mononuclear complex $[Pt(NH_3)_3OH_2]^{2+}$.[13,16] We believe that this can be related to the length of the bridging ligand and the overall charge on the complex. In the case of a short distance between the two Pt(II) centres, as in our complexes, they seem to behave more like +4 charged complexes with a higher electrophilicity (and therefore lower pK_a values) than the corresponding +2 charged complexes. In the case of the two complexes mentioned above, the distance between the Pt(II) centres is longer, with the result that the charges on the Pt(II) centres do not affect each other significantly such that the difference between the pK_a values of the mononuclear and bridged complexes is much smaller.

Interestingly, our complexes display a second deprotonation step with a 1.1 to 1.7 units higher pK_a value, whereas in the case of **1,0,1/t,t,t** and **1,1/t,t**, the pK_a values for the first and second deprotonation steps could not be separated.[13,16] Once again we suggest that the observed interaction between the two Pt(II) centres is due to the shorter distance between the metal atoms as compared to **1,0,1/t,t,t** and **1,1/t,t**. There are several indications that the average distance between the two Pt(II) centres controls the observed ΔpK_a values ($\Delta pK_a = pK_{a2} - pK_{a1}$), *viz.* the weaker the interaction, the smaller the ΔpK_a. Firstly, ΔpK_a for **mPh** is about 0.3 units larger than for **pPh**, which possesses the longest Pt–Pt distance. In case of the aliphatic bridged complexes, ΔpK_a for **But** is 0.2 units smaller than in **Pro**, for which the bridge is one CH_2 group shorter. Secondly, ΔpK_a is smaller for complexes with an aromatic bridge (1.1 and 1.4 for **pPh** and **mPh**, respectively) than for complexes with an aliphatic bridge (1.5 and 1.7 for **But** and **Pro**, respectively). It could be argued that the aromatic bridging ligand possesses shorter C–C distances and should therefore be the shorter bridge and exhibit a larger ΔpK_a. However, it is the average distance between the two Pt(II) centres that is important and not the maximum possible distance. In the case of the aliphatic bridged complexes, many different conformers with shorter Pt–Pt distances exist due to the higher flexibility of the bridging ligand. The higher flexibility as compared to the aromatic bridges leads to a decrease in the average Pt–Pt distance, thereby enabling a stronger interaction between the two Pt(II) centres and a larger ΔpK_a. The same argument holds for the fact that an increase in chain length of the bridging linker by one atom decreases ΔpK_a by about 0.2 units in the case of the complexes with an aliphatic bridge, whereas ΔpK_a is decreased by 0.3 units for the complexes with the inflexible aromatic bridge.

Notwithstanding the developed understanding, the difference in the pK_a values for the **Pro** and **But** complexes still remains puzzling. Based on our observations for the **mPh** and **pPh** complexes, it is reasonable to expect that the pK_a for the first deprotonation step should be the same for **Pro** and **But**. However, the pK_a value for the first complex is 0.4 units higher than for the second complex. Our temperature dependent ^{1}H NMR studies (Fig. 7) suggest that the portion of the species of the chloro complex of **Pro** where all 2-pyridinemethyl groups are stereochemically identical is very low at 25.0 °C, whereas the corresponding chloro complex of **But** mainly exists in this conformation under the same conditions. As a result of the high flexibility of the aliphatic backbone and the short distance between the two chelates attached to the Pt(II) centre, intramolecular π-stacking and/or hydrogen bonding effects can lead to a folded chloro complex of **Pro** at lower temperatures where the 2-pyridinemethyl groups are no longer stereochemically identical and therefore exhibits new ^{1}H NMR signals. This kind of stacking interaction in solution has already been observed for the mononuclear complex [Pt(2,2′:6′,2″-terpyridine)Cl]$^+$, and leads to the formation of π-stacked dimers.[26] We, therefore, expect that the aqua complex **Pro** also exhibits this folding behaviour, with the result that the Pt(II) centres of the folded conformer will certainly possess different properties than the non-folded conformer, which in turn will lead to deviations in the pK_a value and the kinetic parameters reported below.

Kinetics of the reaction with chloride

The first substitution step of the binuclear complexes with chloride is at least 13 times faster than the corresponding reaction with the mononuclear complex. This is in line with the higher electrophilicity of the binuclear Pt(II) centres as also indicated by their lower pK_a values. Since the difference

between the pK_{a1} values of the mono- and binuclear complexes is higher than in the case of **1,1/t,t** and **1,0,1/t,t,t**, it is not surprising that the enhancement of the reaction rate is also larger in our case than for the binuclear complexes **1,1/t,t** and **1,0,1/t,t,t**, which are accelerated by a factor of 6.6 and 1.3, respectively.[13,16] By changing the nature of the bridging ligand, not only the average distance between the two Pt(II) centres is changed, but also the steric and σ-donor properties of the surrounding environment. It is difficult to discuss the absolute values of k_1 and k_2, and we therefore restrict the discussion to the ratio of k_1 and k_2. The second reaction is always 3 to 13 times slower than the first, which is again in line with the lower electrophilicity of the +3 charged intermediate. The ratio of k_1/k_2 for **mPh** and **pPh** (*viz.* 13 and 3, respectively), depends significantly on the distance between the two Pt(II) metal centres, where the ratio becomes smaller for the binuclear complex with the longer bridge. By way of comparison, for **1,1/t,t** where the bridge is longer by two CH_2 groups, there is no measurable difference in the rate constants for the first and second reactions with chloride.[13] Surprisingly, although the difference in the pK_{a1} and pK_{a2} values decreases in going from **Pro** to **But**, indicating that there are less interactions between the two Pt(II) centres, there is no decrease in the ratio of k_1/k_2 for the aliphatic bridged complexes. However, there may be additional contributing effects due to the high flexibility of the backbone, as mentioned above.

Activation parameters

It was recently shown that substitution reactions of the mononuclear complex follow an associative mechanism for various entering nucleophiles.[21] Therefore, it is not surprising that all the observed activation entropies, except those for the first reaction steps of **pPh** and **Pro**, are negative and confirm the associative mechanism. The absolute values of $\Delta S^{\ddagger}$ are rather small since the overall charge of the complex decreases during the reaction with chloride, by which a decrease in electrostriction (*i.e.* increase in entropy) occurs. The small positive value of $\Delta S^{\ddagger}$ for the first reaction of **pPh** is insignificant because of the relatively large error. $\Delta S^{\ddagger}$ is significantly positive for the reaction of **Pro** with chloride, and this is accompanied by the largest $\Delta H^{\ddagger}$ value for the series of complexes, although the corresponding reaction is the fastest among the series. This again emphasizes the extraordinary behaviour of **Pro**, and indicates that further unresolved effects contribute to the reactivity of this complex. In general, $\Delta H^{\ddagger}$ is higher for the mononuclear than for the binuclear complexes, which is in agreement with the observed higher reactivity of the latter. The large difference between the rate constants for the first and second substitution reactions of the **mPh** complex is also reflected in the activation enthalpies; $\Delta H_1^{\ddagger}$ is 5 kJ mol^{-1} smaller than $\Delta H_2^{\ddagger}$. For the complexes with the longer bridges, **pPh** and **But**, where k_1 and k_2 are closer together, no significant difference between $\Delta H_1^{\ddagger}$ and $\Delta H_2^{\ddagger}$ can be observed. This leads to the conclusion that the effect of the interaction of the two Pt(II) centres on the values of $\Delta H^{\ddagger}$ for longer Pt–Pt distances is too small to be measured accurately since the experimental error limits are larger than the expected differences in $\Delta H^{\ddagger}$.

Conclusions

It could be shown that the lability of the binuclear bridged complexes **mPh**, **pPh**, **Pro** and **But** differs significantly from that of the corresponding mononuclear complex. This can be accounted for in terms of an enhanced electrophilicity of the binuclear Pt(II) centres. In addition, the reactivity of one Pt(II) centre depends on the state of the other Pt(II) centre, which results in different thermodynamic and kinetic properties for the first and second reaction steps. The interactions between the two Pt(II) centres depend on the Pt–Pt distance; the closer the proximity of the two metal centres, the larger the interaction between them. Based on these observations, it is suggested that the observed interaction does not result from an electronic effect mediated by the bridging ligand, since a larger difference between the behaviour of the aromatic (sp^2) and aliphatic (sp^3) bridged complexes would be expected. This is not surprising, since the X-ray structures of other metal complexes with such bridging ligands indicate that the aromatic ring is almost perpendicular to the plane of the complex,[18,27] and therefore the interaction between the metal centre and the π-electrons of the benzene ring is very small. Electrostatic repulsive effects are suggested to account for the observed trends, in terms of which electrophilic properties of one Pt(II) centre depend largely on the charge (+2 or +1) of the neighbouring Pt(II) centre. This kind of electrostatic effect is already long known to be responsible for the two pK_a values observed for the dissociation of aliphatic dicarboxylic acids, where ΔpK_a is inversely proportional to the average distance (considering the flexibility of the aliphatic linker) between the two reaction centres.[28–32] In addition, it is suggested that the unusual results obtained for the **Pro** complex are due to the existence of folded conformer(s) in solution at 25 °C, which have different properties than the corresponding symmetric complexes. In order to fully understand the influence of aliphatic chain length effects on the binuclear complexes in terms of their folding abilities or the average Pt–Pt distance and interactions, a wider range of bridging ligands will have to be studied in future.

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